Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

Final scope

Final remit/evaluation objective

To appraise the clinical and cost effectiveness of garadacimab within its marketing authorisation for preventing recurrent attacks of hereditary angioedema.

Background

Hereditary angioedema (HAE) is a rare genetic disorder, associated with the deficiency of the protein C1-esterase inhibitor, which is a regulator of inflammatory pathways. Normally, C1-esterase inhibitor controls the enzyme cascade reactions so that uncontrolled swelling of the subcutaneous and submucosal tissues do not occur. In patients with HAE, at times of physiological or psychological stress, the function of the C1-esterase inhibitor is insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings. The swellings often occur in the mouth, the gut (affecting the submucosal tissues) and the airway, causing difficulty with breathing (with potential asphyxia) and severe pain in the stomach. The swellings can also occur in the deep tissues of the skin (affecting the dermis and subcutaneous tissues) causing significant impact, for example if the hands, feet or genitals are affected. HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety.

Many angioedema attacks are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors. But often, a specific trigger cannot be identified. Attacks are unpredictable; severity and frequency of previous attacks do not predict severity and frequency of future attacks. Attacks usually last approximately 2 to 5 days before resolving spontaneously.

There are 3 types of HAE. Types I (85%) and II (15%) are a result of a known genetic mutation and account for almost all cases of HAE[1]:

- type I is defined by low levels of a normal protein C1-esterase inhibitor in the plasma.
- type II is defined by normal level of a dysfunctional protein C1-esterase inhibitor in the plasma.
- HAE with normal C1 inhibitor (previously referred to as type III) is not a result of the deficiency of protein C1-esterase inhibitor. However, it is known that oestrogen has a role not yet fully understood.[2]

It is estimated that type I and type II HAE affect at least 1 per 59,000 of the UK population and can affect people of any ethnic group or gender.[1,3] HAE usually presents in childhood, with the mean age of onset being between 8 and 12 years.

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Attacks rarely occur before two years of age and are less frequent before adolescence.[1]

There are 3 approaches to managing HAE: avoidance of factors that trigger HAE (e.g. minor trauma, hormone replacement therapy), acute treatments and preventive (prophylactic) treatments of acute attacks. Short-term preventive treatments aim to prevent an attack before known triggers for example, dental work or surgery. Long-term preventative treatments are used routinely to reduce the need for treatment of acute attacks. As a long-term strategy attenuated androgens or C1-esterase inhibitors (C1-INH) such as Cinryze, Ruconest or Berinert can be used. Anti-fibrinolytics, such as tranexamic acid, can also be used.

NICE Technology Appraisal 606 recommends lanadelumab for preventing recurrent attacks of hereditary angioedema in people aged 12 and older, only if they are eligible for preventative C1-INH in line with NHS England's commissioning policy and the lowest dosing frequency of lanadelumab is used when the condition is in a stable, attack-free phase.

NICE Technology Appraisal 738 recommends berotralstat for preventing recurrent attacks of hereditary angioedema in people 12 years and older, only if they have at least 2 attacks per month and it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.

The technology

Garadacimab (brand name unknown, CSL Behring) does not currently have a marketing authorisation in the UK for preventing recurrent attacks of hereditary angioedema in people 12 years and over. It has been studied in phase 3 clinical trials to prevent HAE attacks in people 12 years and over with a clinical diagnosis of C1-inhibitor (type I or type II) HAE.

Intervention(s)	Garadacimab
Population(s)	People 12 years and over with hereditary angioedema
Comparators	Established clinical management for preventing attacks of hereditary angioedema which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Attenuated androgens • Antifibrinolytics • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat

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Outcomes	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • attack-free period • time to first attack • need for acute treatment • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Berotralstat for preventing recurrent attacks of hereditary angioedema (2021) NICE technology appraisal guidance 738. Lanadelumab for preventing recurrent attacks of hereditary angioedema (2019) NICE technology appraisal guidance 606.
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2023) Manual for prescribed specialist services (2023/2024) chapter 59, 115 and 115A NHS England (2016) Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema(HAE) types I and II

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References

1. NHS Clinical commissioning: plasma derived C1-esterase inhibitor for prophylactic treatment of HAE (2016). Accessed May 2024 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf

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3. Yong PFK, Coulter T, El-Shanawany T, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. Journal of Allergy and Clinical Immunology: In Practice. 2023.